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A longitudinal study of serial BODE indices in predicting mortality and readmissions for COPD

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KEYWORDS
COPD;
Serial BODE index;
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Summary
Introduction: BODE index comprises Body mass index, Obstruction of the airway [FEV_1], Dyspnoea score [modified Medical Research Council questionnaire] and Exercise capacity [6 min walk test]. This study assessed the role of serial changes in BODE index in predicting mortality and readmissions of COPD patients.
Methods: A prospective cohort study involving 243(208males) COPD patients hospitalized for acute exacerbations of COPD [AECOPD]. BODE index was assessed at 6 weeks(baseline), 6, 12, 18 and 24 months post hospital discharge. Mortality and readmissions in the subsequent 3 years were recorded. All the patients were managed by usual care without additional intervention.
Results: The mean (SD) age and FEV_1% predicted were 74.2(7.8) yrs and 51.7(21.6)% respectively. Over the 3 years, 25.1% died whereas 76.5% had at least 1 readmission for AECOPD. Baseline BODE index was predictive of both the survival and readmissions to hospital for AECOPD by Cox regression analysis ($p < 0.001$ for both survival and readmissions). Over 24 months, 71(40.1%), 94 (53.1%), 12(6.8%) patients had increased (>1point), no change, and decreased in BODE (>1point) index respectively. Serial changes in BODE index at 6 month was marginally associated with mortality, but not at 12-, 18- and 24-month. The 6-, 12- and 24-month BODE indices were predictive of the readmissions for AECOPD when compared to baseline.

Abbreviations: 6-MWT, 6-min walk test; AECOPD, acute exacerbations of COPD; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled steroid; LABA, long acting beta-agonist; mMRC, modified Medical Research Council.

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Conclusion: Baseline BODE index could predict both survival and readmissions for AECOPD, whereas serial BODE indices were not predictive of survival at 3 years. Single rather than serial measurements of BODE index is sufficient for prediction of survival and readmissions for patients treated with usual care.

Introduction

COPD is a common disease worldwide with a high burden on healthcare resources.[1,2] The prevalence of COPD varied from 11.4 to 26.1% according to a recent multi-city population study using spirometry.[1] In Hong Kong, the prevalence rates of COPD in the elderly population aged ≥60 years were 25.9% and 12.4% based on the spirometric definition of forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <70% and the lower limit of normal of the FEV_1/FVC respectively.[3] In 2005, the crude mortality rate of COPD was 29.1/100,000, while the crude hospitalization rate was 193/100,000 in Hong Kong.[4] In Hong Kong, COPD ranked second as a respiratory cause for hospitalization and inpatient bed-days. In those 75 years or older, the hospitalization rate for COPD was as high as 2225/100,000.[4] The economic burden of COPD on the society is enormous.[5,6]

The BODE index, a simple multidimensional grading system, was developed in 2004 by Celli and colleagues, for predicting mortality risk of COPD patients. The BODE index included the body mass index (B), degree of airflow obstruction (O) measured by FEV_1, dyspnea (D) measured by a simple dyspnea questionnaire,[7] and exercise capacity (E) measured by the 6-min—walk test.[8] Studies have shown that BODE index could predict mortality better in COPD patients than FEV_1 alone.[8,9] Subsequent studies also demonstrated that BODE index could predict hospital admissions for COPD.[10,11]

All except one previous study on BODE index focused on the index at one time point and its predictive power on mortality, exacerbations and hospital readmissions of COPD.[8,10,12] The only study that involved serial BODE indices on mortality assessed patients who were treated with either lung volume reduction surgery or best medical care.[13] There are currently no data on the ability of serial changes in BODE indices for predicting the mortality and readmissions for COPD patients in those who were treated with usual care (real life treatment, not necessarily the best medical treatment according to guidelines[14,15]). This study assessed the role of serial BODE indices in predicting the mortality and hospitalizations of COPD subjects who were treated with usual care over a 3 year period.

Material and methods

This was a prospective study of patients who had been admitted to the Prince of Wales Hospital with acute exacerbations of COPD (AECOPD) between May 1, 2004, and April 30, 2005. AECOPD was defined as occurring when a patient with background COPD,[14] with FEV_1/FVC ratio <70%, presented with at least two major symptoms (increased dyspnea, increased sputum purulence, or increased sputum volume), or one major and one minor symptom (nasal discharge/congestion, wheeze, sore throat, or cough) for at least 2 consecutive days.[16—19] Written informed consent was obtained from each subject, and the study was approved by the Ethics Committee of the Chinese University of Hong Kong.

Upon discharge from hospital, subjects attended the pulmonary function laboratory for assessment at 6—8 weeks (baseline), 6 months, 12 months, 18 months, and 24 months. BODE index was measured at each visit and hospital admissions were recorded. At the baseline assessment, the demographic characteristics and the medication usage of the subjects were recorded. Co-morbid conditions were scored using the Charlson index[20] which ranged from 0 to 33, with a higher score indicating more in the number and severity of the coexisting illnesses.

Telephone follow-up to check for any hospital admissions or death was arranged for subjects who did not return for assessment. At the end of the 3 years, patients were contacted by phone to assess for readmissions and mortality. Hospital records were also reviewed at the end of the study. Any readmissions and the cause of death would be recorded. These subjects were treated with usual care with no specific intervention. No pulmonary rehabilitation was offered except for those subjects who could not be discharged directly. These subjects would be transferred to convalescent hospital for a short course (usually for a week) of inpatient pulmonary rehabilitation.

Table 1 Calculation of the BODE index. The total possible values range from 0 to 10.

Variable	Points in BODE index			
	0	1	2	3
FEV_1 (% of predicted)	≥65	50—64	36—49	≤35
Distance walked in 6 min (m)	≥350	250—349	150—249	≤149
mMRC dyspnoea scale	0—1	2	3	4
Body Mass Index (kg/m^2)	>21	≤21		

mMRC = Modified Medical Research Council.

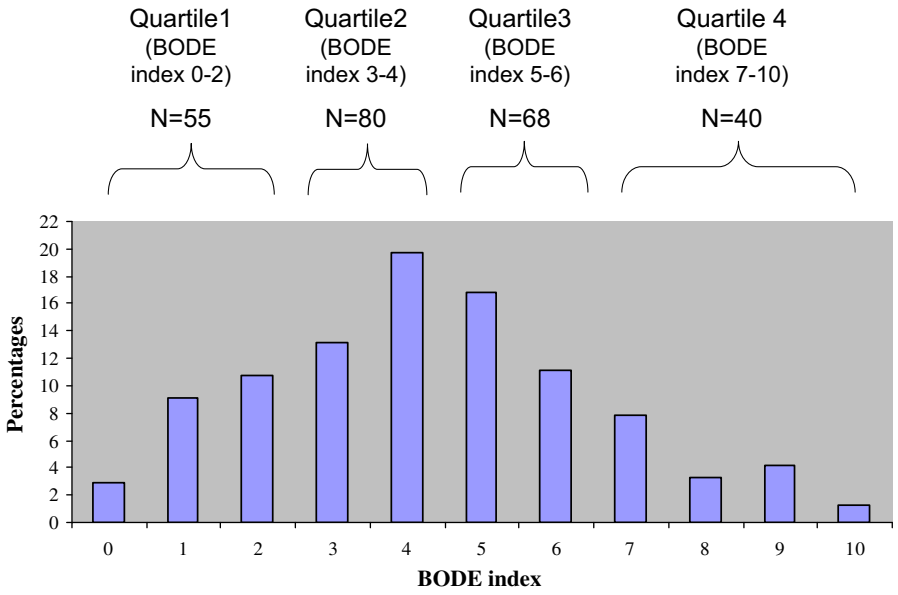

Figure 1 Distribution of the BODE index of the subjects at baseline ($n = 243$).

Table 2 Demographic characteristics of the subjects ($n = 243$).

Age (years)		74.22 ± 7.80
Sex	Male	208(85.6%)
	Female	35(14.4%)
Smoking status	Current smoker	61(25.1%)
	Ex-smoker	181(74.5%)
	Non-smoker	1(0.4%)
Premorbid status	Chair bound	2(0.8%)
	Home bound	12(4.9%)
	Could walk on level ground	50(20.6%)
	Could walk up at least one flight of stairs	179(73.7%)
BMI (kg/m^2)		21.41 ± 4.70
FEV_1 (L)[b]		0.87 ± 0.38
FEV_1% predicted[b]		51.70 ± 21.59
FEV_1/FVC ratio[b]		57.58 ± 14.85
mMRC dyspnoea score		1.8 ± 0.9
6 min walk test (m)[a]		262.3 ± 99.0
No. of hospitalizations in the previous 12 months		1.17 ± 1.63
Home oxygen use		21/243 (8.6%)
Home NPPV use		2/243 (0.8%)
Medications use	ICS	108/243 (44.4%)
	LABA	5/243(2.06%)
	Long acting anti-cholinergic	1/243 (0.41%)
	Theophylline	79/242 (32.6%)
	Influenza vaccination in the past 12 months	83/243 (34.2%)
Comorbidities	Charlson index	1.45 ± 0.82
	Diabetes mellitus	29/243 (11.9%)
	Hypertension	76/243 (31.3%)
	Ischaemic Heart disease	20/243 (8.2%)
	Cerebrovascular disease	8/243 (3.3%)

Data are presented in mean ± SD or *n* (%).
BMI: body mass index.
MMRC: modified Medical Research Council.
NPPV: non-invasive positive pressure ventilation.
[a] $n = 243$.
[b] post-bronchodilator measurements.

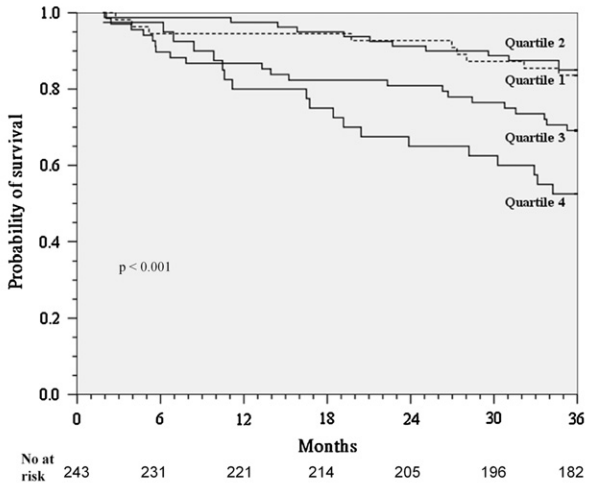

Figure 2 Kaplan—Meier survival curves for the four quartiles of the BODE index and survival.

Measurement of the BODE index

Weight and height were measured to compute the Body Mass Index, Obstruction of the airway was assessed by spirometry before and after bronchodilator therapy (20 min after inhaling 400 mg of salbultamol through a 500 mL spacer [Ventolin; GlaxoSmithKline, Evreux, France]) according to the American Thoracic Society standard[21] using a spirometer (Vitalograph; Buckingham, UK). The updated predicted spirometry values for Hong Kong Chinese were adopted.[22] The degree of Dyspnoea was measured by the modified Medical Research Council (mMRC) questionnaire with a score ranging from 0—4.[7] Exercise capacity was measured by 6-min walk test (6-MWT).[23] The BODE index, an 11 point composite score (0 through 10) was then computed as shown in Table 1 according to Celli et al.[8]

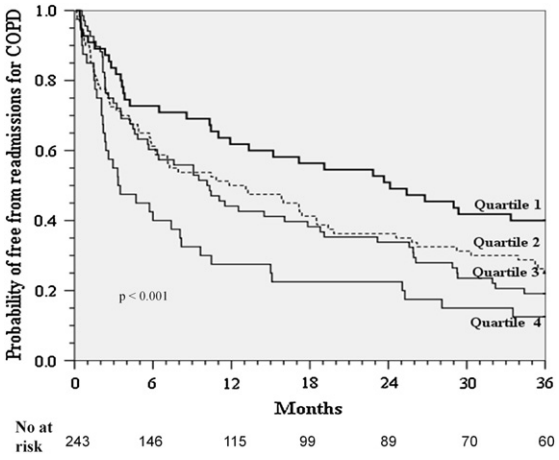

Figure 3 Kaplan—Meier survival curves of the baseline BODE index and first readmissions for AECOPD.

Satistics

Data were analyzed using a statistical software package (SPSS for Windows, version 13.0; SPSS Inc; Chicago, IL). Data for continuous variables were presented as means [SD]. Cox proportional hazards regression analyses were used to assess the capacity of BODE index to predict the risk of mortality.[24] The predictive characteristics of the baseline BODE index for survival and first readmission for AECOPD were assessed by Kaplan—Meier analysis according to quartiles of the BODE index and the statistical significance was evaluated by the log-rank test. The predictive characteristics of the changes in serial BODE indices for survival and first readmission of AECOPD were assessed by Kaplan—Meier analysis (serial change at a certain time point was classified as having decreasing [>−1point], stable or increasing [>+1point] BODE indices based on their absolute change from baseline) and statistical significance was evaluated with the use of the log-rank test. The index of concordance was used to directly compare the predictive ability of the baseline BODE index and its separate components on mortality and first readmission for AECOPD.

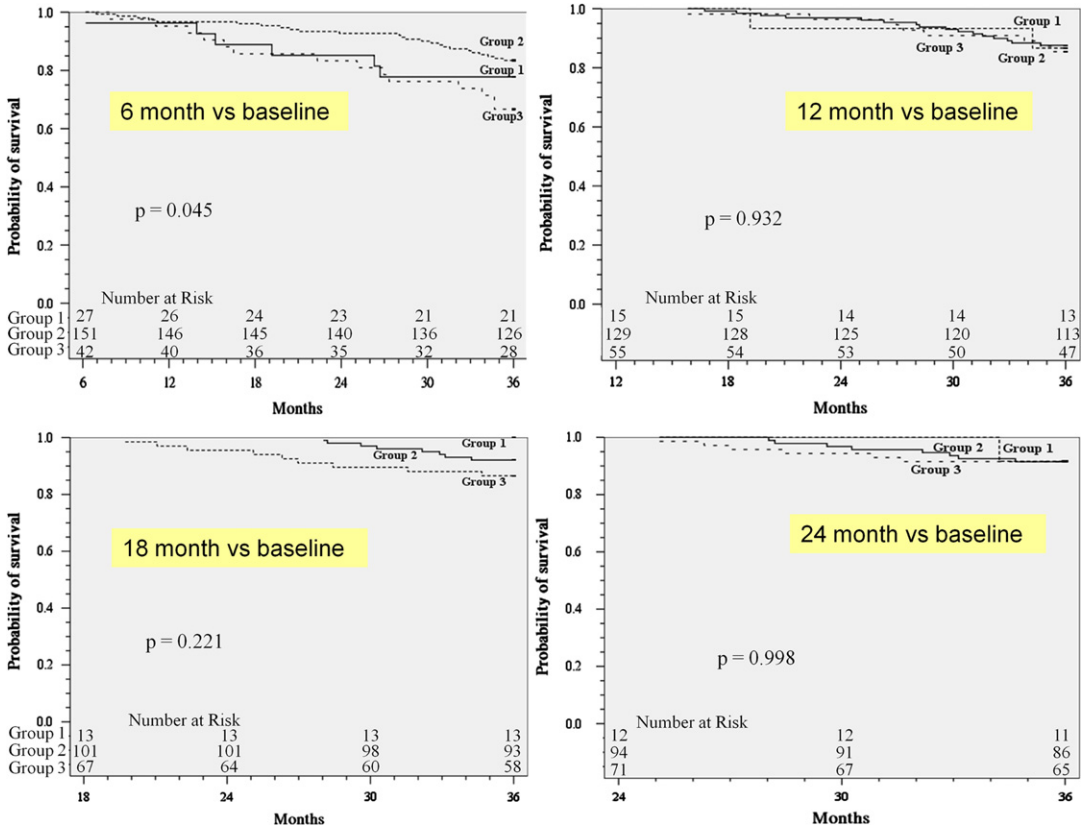

Figure 4 Kaplan—Meier survival curves showing the changes in BODE index over time and survival. Group 1: BODE index decreased by >1 point; Group 2: Stable BODE index; Group 3:BODE index increased by >1 point.

Results

Altogether 327 subjects were recruited for this study. As 20 subjects could not perform satisfactory spirometry whereas 64 subjects were unable to perform 6-MWT (either too breathless to walk, having arthritis or old cerebrovascular accident that limited their mobility) at the baseline study, we have only included 243 subjects for our analysis. The mean [SD] age was 74.2[7.8] yrs with moderate airflow obstruction (post-bronchodilator FEV_1% predicted was 51.7 [21.6]%). The majority of the subjects were current smokers (25.1%) or ex-smokers (74.5%) with smoking history of 52.3[23.6] and 44.0[25.6] pack years respectively.

A significant number (69.5%[169/243]) of patients had co-morbidity (11.9%, 31.3%, 8.2% and 3.3% with diabetes mellitus, hypertension, ischaemic heart disease and old cerebrovascular accident respectively) and about half of them were on inhaled corticosteroid with an average dose of 1329.1[604.5] mcg of beclomethasone dipropionate equivalent per day. The mean (SD) BODE index at baseline was 4.30 (2.25) and its distribution is shown in Fig. 1. With usual care, the mean (SD) 6, 12, 18 and 24 month BODE indices were 4.4(2.5), 4.7(2.6), 5.1(2.5) and 5.2(2.6) respectively. Using a 1-point difference as the cut-off, 40.1%, 53.1% and 6.8% of the patients had increased (>1point), no change (≤change in 1 point), and decreased in BODE (>1point) index over 24 months respectively. Using a 2 point difference, 19.8%, 78.5%, 1.7% patients had increased (>2 points), no change (change in ≤2 points), and decreased in BODE index (>2 points) over 24 months respectively. The mean values and changes of BODE index over time are shown in Table 2.

Over the 3 years, 25.1%(61/243) had died. There was no difference in the mortality between the current smokers and ex-smokers (24.9% [45/181] vs 26.2% [16/61], $p = 0.83$) Among the deceased, 29.5%(18/61), 6.6%(4/61), 13.1%(8/61) died of COPD, pneumonia, and lung cancer respectively. The non-pulmonary causes of death included 6 malignancies (1 esophagus, 1 stomach, 2 large bowel, 1 cholangiocarcinoma, 1 hepatocellular carcinoma), 2 acute myocardial infarction, 2 biliary sepsis, 1 cerebrovascular accident, 1 gastrointestinal bleeding, 1 intestinal obstruction, 1 perforation of colon, 1 acute renal failure, 15 sudden death and 1 suicide. Subjects had on average (SD) 3.37(3.80) admissions (range 0—25) over 3 years whereas 76.5%(186/243) had at least 1 readmission for AECOPD.

Patients with higher baseline BODE scores were at higher risk for death and readmission; the hazard ratios for death and readmissions from any cause per one-point increase in the baseline BODE score were 1.25 (95% CI, 1.12—1.39; $P < 0.001$) and 1.12(95% CI, 1.05—1.20; $P < 0.001$) respectively. When stratifying the baseline BODE index into 4 quartiles (first quartile with a BODE index of 0—2, second quartile 3—4, third quartile 5—6, fourth quartile 7—10),[8] there were significant differences in the mortality rates among the quartiles ($p < 0.001$), with a higher BODE score

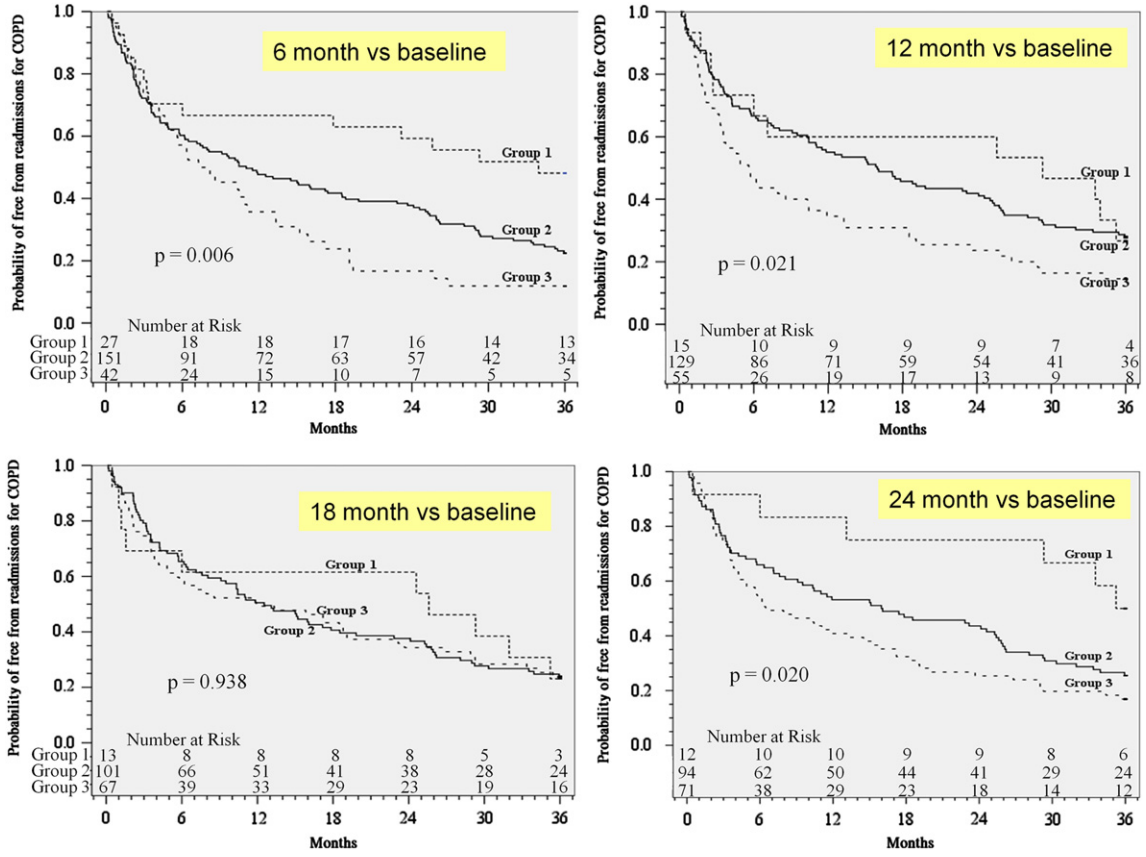

Figure 5 Kaplan–Meier survival curves showing the changes in BODE index over time and readmissions for COPD. Group 1: BODE index decreased by >1 point; Group 2: Stable BODE index; Group 3:BODE index increased by >1 point.

showing a higher mortality over time. Similar pattern was observed for the relationship between baseline BODE index and first hospital readmissions for AECOPD with earlier readmissions among those with higher BODE scores. Baseline BODE index also correlated weakly with the number of readmissions over 3 years ($r = 0.301$, $p < 0.001$). The Kaplan–Meier Curves for both the mortality and first readmissions and the four quartiles of the baseline BODE index are shown in Figs. 2 and 3.

Serial change of BODE index (>+1 point, static or >−1 point) was marginally predictive of mortality when the 6th month BODE index was compared with the baseline BODE index. However, the serial change of BODE index was not predictive of the mortality when the 12th, 18th and 24th months BODE indices were compared with the baseline line BODE index (Fig. 4). The 6th, 12th and 24th month BODE indices when compared to the baseline BODE index however showed that patients with increased BODE index of >1 point had earlier readmissions to hospital than those with static or decreasing BODE index (Fig. 5). The 18th month BODE index when compared with the baseline BODE index were not predictive of readmissions for AECOPD.

The concordance indices of the baseline BODE index in predicting survival and readmissions at 36 months are shown in Table 4. The index of concordance allows us to quantify the predictive ability of a survival model. Baseline BODE index

Table 3 BODE index of our subjects at different time points.

Time Point		Baseline	6 month	12 month	18 month	24 month
n		243	220	199	181	177
BODE index		4.30 ± 2.25	4.44 ± 2.54	4.71 ± 2.61	5.14 ± 2.55	5.20 ± 2.61
Change in BODE index[a]	Increased >1 point		42 (19.1%)	55 (27.7%)	67 (37.0%)	71(40.1%)
	No change		151(68.6%)	129 (64.8%)	101 (55.8%)	94 (53.1%)
	Decreased >1 point		27(12.3%)	15 (7.5%)	13 (7.2%)	12 (6.8%)
With missing BODE index (excluding death), *n*		0	7	9	18	20
Subjects died, *n*			16	35	44	46

Data are presented in mean ± SD or *n* (%).
[a] compared with baseline line.

Table 4 The concordance indices of the baseline BODE index in predicting survival and first readmissions over 3 years (n = 307).

Baseline variables	Survival	First readmission
BODE index	0.68	0.58
Post-bronchodilator FEV_1 (% predicted)	0.64	0.60
6 min walk distance (m)	0.66	0.54
BMI (kg/m^2)	0.65	0.56
mMRC score	0.66	0.57

BMI = body mass index; mMRC = modified Medical Research Council.

could predict the survival of the COPD patients better than post-bronchodilator FEV_1% predicted, BMI, 6-MWT and MMRC score alone. However, for prediction of the first readmissions for AECOPD, post-bronchodilator FEV_1% predicted alone appeared to do better than the BODE index at baseline.

Discussion

This study has shown that with usual care and no additional intervention, baseline BODE index could predict both the mortality and readmissions for AECOPD in our group of COPD patients who had a high rate of mortality and morbidity. For those subjects with a baseline BODE index in the 4th quartile (BODE index score of 7–10), half of the subjects died in 3 years. By 3 years, almost 80% of the subjects had at least 1 readmission for AECOPD. The serial changes of BODE index of the surviving patients, however, did not show any relationship with survival but appeared to have some predictive effect on readmissions. Similar to previous studies, the baseline BODE index predicted mortality more accurately than FEV_1 alone.[8]

In a study that had assessed serial changes in BODE index over time by comparing one group of COPD patients being treated with lung volume reduction surgery against another group that was treated with maximal medical therapy, Martinez et al have shown that an increase in the modified BODE index was associated with increased mortality in both groups of subjects, particularly in the medical treatment group.[13] In addition, a decrease in modified BODE of more than 1 point was predictive of lower mortality in the entire cohort and, particularly, the surgically treated cohort.[13] This study however did not address the relationship between the change in serial BODE index and readmissions for AECOPD.[13] Subjects in our current study were different from those in Martinez et al's study as none of our patients had received lung volume reduction surgery and our patients were just treated with usual medical care. The majority of the patients in our study did not receive long acting beta-agonist (LABA), long acting anti-cholinergic therapy or a combination of inhaled steroid (ICS) and LABA therapy (See Table 2). Our patients also did not receive proper pulmonary rehabilitation programme. In the "real" world, a lot of COPD patients were not treated according to the guidelines due to limited healthcare budget.[25] It is interesting that under usual care, patients did not have much change in their BODE index over a 3 year period in our study (the mean levels were similar over the different time points [Table 3]). This might be the reason why the baseline BODE index could predict mortality whereas serial BODE indices could not.

To the best of our knowledge, this is the first study to assess the role of BODE index among Chinese COPD patients and we found that, similar to the western population, a cross-sectional BODE index could predict overall mortality and the hospital readmission for COPD over a period of 3 years. Interestingly, the hazard ratio for change of 1 point of the baseline BODE index in relationship to the mortality in this current study was similar to the study by Celli et al.[8] It appears that the BODE index is applicable to both the Caucasians and Chinese COPD subjects using the same cut-off values for calculation.

AECOPD leads to significant morbidity and mortality worldwide.[14] Previous studies[16,26] have shown that pulmonary function and quality of life were adversely affected by frequent exacerbations, particularly in active smokers. Studies have shown that a number of factors including infection,[18,19,27–29] outdoor air pollution,[30,31] withdrawal of medications[32] and changes in temperature[33] were associated with AECOPD. This study concurs with previous studies[10,34] that the baseline BODE index of COPD patients is capable of predicting COPD-related hospitalization.[10,11] The mechanisms underlying AECOPD are poorly understood, and it is important to identify factors that help predicting their occurrences.[35] It is likely that the changes in serial BODE indices of the patients would interact with the above mentioned factors (such as infectious agents, changes in level of pollutants, temperature and drug regime), and together with the presence of co-morbidity, could increase the likelihood of developing AECOPD and its related hospitalizations. This could possibility explain why serial BODE indices alone, without taking all these factors into account, could not reliably predict admissions for AECOPD in our study. Studies to assess the interactions of serial BODE indices with the above mentioned factors would be interesting and potentially useful for better understanding of mechanisms of AECOPD.

This study was limited by the fact that this was a single center study and our subjects were in general "sicker" as they were recruited after recovery from an episode of AECOPD that required hospitalization. However, it is important to understand the natural history and the predictor of morbidity and mortality of this group of subjects as they were the main group of COPD subjects that accounted for most of the burden of COPD on the healthcare utilization. When assessing the morbidity of the subjects, we only captured the hospitalization episodes, but not the emergency room visits and primary care visits. It is unlikely that the mortality and hospitalization data were subjected to recall bias as we had obtained the information not only from the subjects, but cross checked with the hospital records.

In conclusion, a single measurement of BODE index could predict mortality and readmissions of COPD patients over time. Serial measurements of the BODE index six monthly for 2 years were not useful for predicting mortality but appeared to have some predictive effect on readmissions in a group of patients treated with usual care.

Conflict of interest

All authors have no conflict of interest to disclose.

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